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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,673	06/03/2002	Howard Green	H0535/7014	6874

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,673	GREEN ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,24,36,51 and 95-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,24,36,51 and 95-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-10, 24, 36, 51 and 95-111 in the reply filed on 4/25/05 is acknowledged. The traversal is on the ground(s) that a search and examination of all of the presented claims would not require an undue burden of searching. This is not found persuasive because it was shown in the Office action mailed on 3/24/05 that the claims presented multiple inventions that do not fall under PCT Rule 13 such that the different inventions are not overlapping in scope and require separate searches. The groups of inventions also lack unity because Urry (US 4,589,882) disclose the claimed special technical feature, the attachment of a tissue to an agent by lysyl oxidase cross-linking. Furthermore, Applicant has cancelled the traversed claims.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-10, 24, 36, 51 and 95-111 are presented for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-10, 36, 102 and 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 9 are rejected because the claims refer to a "complementary linker" but it is unclear what the linker complements.

Claim 36 is rejected be the phrase "an isolated form" is vague and indefinite because it is unclear from what the agent is isolated and what type of form would make the agent isolated.

The term "rich" in claims 10, 102 and 103 is a relative term which renders the claim indefinite. The term "rich" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how many peptide residues meets the limitation "rich".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, 8-10, 24, 96-106, 108 and 109 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Stedronsky (US 6,258,872) in light of Webster's Dictionary.

Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule between said tissue and the adhesive/sealant. The primer molecule can be tissue-associated proteins such as collagen, actin, myosin, proteins or oligopeptides (col. 3, lines 1-5). Stedronsky teaches that separate moieties of the primer molecule are attached to the damaged tissue and the adhesive/sealant by covalent

or non-covalent means. Covalent means include enzymatic cross-linking of the primer and the damaged tissue by any of the following enzymes: is lysyl oxidase, a transglutaminase, a phosphorylase, a glycosylase or a fatty acetyltransferase (col. 8, lines 33-41). This disclosure meets the limitations of instant claim 1 because Stedronsky teaches the attachment of an agent (an adhesive/sealant) to a body tissue via a linker (the disclosed primer) by cross-linking with lysyl oxidase. The primer molecule strengthens the interaction between the damaged tissue and adhesive/sealant because the primer molecule interacts with the proteins in the tissue, thereby altering the characteristics of the tissue to make it more amenable to binding with the adhesive/sealant matrix (abstract).

The order of the attachment of the primer to the adhesive/sealant and the body tissue can vary. The tissue adhesive/sealant and the primer can be cross-linked by the enzyme in a first step. The product of this reaction can then be attached to the damaged tissue by the same enzymatic reaction, as required by the limitations regarding the order of steps in instant claim 24. Alternatively, the primer can be attached to the damaged tissue in a first step, as required by instant claims 2, 8 and 9, and subsequently the adhesive/sealant is then cross-linked to the primer-bound tissue. Both reactions are catalyzed by an enzyme (col. 8, lines 51-65). The enzyme cross-linker Stedronsky states that the disclosed invention can improve the performance of any tissue adhesive/sealant which is capable of bonding to any anatomical site (col. 7, lines 1-7). Stedronsky provides examples for tissues such as skin, bone, tendon or cartilage as substrates to which the primer and adhesive/sealant are applied according directions of the disclosed invention (col. 9 and 10). This disclosure of skin as a body tissue meets the limitations of instant claim 98. The teaching of an adhesive/sealant satisfies the limitation of instant claims 98, 99, 101 and 104, wherein the agent is a pharmaceutical agent and is not a microparticle. The disclosure that teaches that the primer molecule can be tissue-associated proteins such as collagen, actin, myosin, proteins or oligopeptides (col. 3, lines 1-5) meets the limitation of instant claims 3 and 10 because named proteins for the primer (linker) all bear at least one amine, such as lysine. Claims 10 and 102 require that the linker is a protein rich in lysine. The disclosed primers (linkers) can be a protein such as collagen which has lysyl groups *supra*.

This disclosure meets the limitation of "rich" in claims 10 and 102 since "rich" is interpreted, in the absence of guidance from the instant specification, to mean at least one. The adhesive/sealant is a synthetic polymer such as polyethylene glycol, polyesters and polyvinyl alcohols (col. 7, lines 10-15). These materials are nonprotein, not substrates of lysine oxidase, nor do they react with other lysine oxidase substrates, thus meeting the limitations of claims 100, 96 and 97, respectively. The synthetic polymer can further comprise proteins that can comprise one or more reactive functionalities such as one or more amino groups (i.e. lysine) or carboxyl groups (i.e. aspartate or glutamate) for cross-linking purposes (col. 7, lines 15-25). This disclosure meets the limitation of "a polymer rich in lysine" in claim 103 since "rich" is interpreted, in the absence of guidance from the instant specification, to mean at least one.

The disclosure by Stedronsky meets the claims limitations regarding the "microparticle" because Webster's defines s "particle" as a tiny piece or part (p. 857). The disclosed tissue sealants are comprised of polymers which are small pieces of matter. The limitation of "nonplanar" is satisfied because a space filling molecular model would demonstrate that any of the polymers taught by Stedronsky have an uneven surface. Furthermore, it is noted that the language or claim 51 is "open" (comprising). Therefore, the microparticle can have additional components and still meet the limitations of instant claim 51. The primer, which is inserted between the tissue and the agent (microparticle) can be considered as part of the microparticle or an additional component. Either interpretation meets the claim 51.

The disclosure by Webster's Dictionary is a supporting reference and properly used in a rejection under of U.S.C. 102 since it describes the definition of a particle. MPEP 2131.01.

Claims 36 and 107 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Urry (US 4,589,882).

Urry discloses the application of bioelastic polymers to tissue to the repair of damage to said tissue. The polymers are natural substrates of lysyl oxidase which is naturally occurring in tissue. The

lysyl oxidase present in the tissue is sufficient to cause the cross-linking of the bioelastomeric polypeptides and the tissue (col. 7, lines 25-55). This disclosure meets the limitations of instant claim 36 because bioelastomers comprise amine groups that are substrates for lysyl oxidase, they are applied to a body tissue and the lysyl oxidase present in the tissue is sufficient to cause cross-linking. It is noted that the claim only requires that the lysyl oxidase is present, it does not specify that it was exogenously added. Urry teaches that bioelastomers are polypeptides of 1-10 helix-forming amino acid residues (col. 2, lines 45-68). A protein generally has 100 or more residues. Therefore, bioelastomers are non-protein and meet the limitation of instant claim 107.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 24 and 95-106 rejected under 35 U.S.C. 103(a) as being unpatentable over Stedronsky (US 6,258,872), as applied to claims 1-3, 8-10, 24 and 96-104, in view of Takahara et al. (US 6,010,871).

Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule between said tissue and the adhesive/sealant. The primer molecule is the primer molecule can be tissue-associated proteins such as collagen, actin, myosin, proteins or oligopeptides.

Stedronsky does not teach that the primer is a polymer having at least four contiguous lysine residues.

Takahara et al. disclose that polylysine can be attached to physiologically active proteins or DNA by transglutaminase (col. 4, lines 23-40 and col. 8, lines 43-58). Polylysine serves as a spacer between a targeting molecule and the biological active component such as DNA. Polylysine is advantageous because is harmless to living bodies. This disclosure meets the limitations of instant claims 4-7 and 95 because polylysine consists of only lysine residues and thus meets the limitations regarding the minimum number of contiguous lysine residues and percent lysine residues.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ polylysine as a primer (spacer) in the invention of Stedronsky. The ordinary artisan would have been motivated to do so because polylysine is a safe and well known linking agent for pharmaceutical delivery *in vivo* and would serve as an equivalent alternative for the protein primers taught by Stedronsky. The ordinary artisan would have had a reasonable expectation that polylysine would successfully serve as a primer in the invention taught by Stedronsky because it is an inert linker that can be attached to biologically active agents by transglutaminase. The teaching of transglutaminase meets the lysine oxidase of the instant claims because Stedronsky taught that lysine oxidase and transglutaminase are both suitable cross-linking enzymes.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10, 24, 36, 51 and 95-108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 and 48 of U.S. Patent No. 6,267,957 in view of Stedronsky (US 6,258,872) and Webster's Dictionary.

The claims of '957 are drawn to a method for attaching a non-corneocyte protein, an agent, to a body comprising conjugating the agent to a carboxamide -containing linking molecule and then attaching he linked agent to the body tissue via transglutaminase. The claims meet the limitation in the instant application regarding the term "microparticle" because a microparticle is interpreted as a small part *supra* and non-corneocyte proteins are small parts of matter. '957 does not claim the employment of lysine oxidase to effect the crosslinking reactions. Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule, such as a protein, between said tissue and the adhesive/sealant. The agents can be cross-linked together by transglutaminase or lysine oxidase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute lysine oxidase for transglutaminase in the invention of '957. The ordinary artisan would have been motivated to do so because lysine oxidase and transglutaminase are equivalent alternatives for cross-linking of biological agents and proteins. The ordinary artisan would have had a reasonable

expectation that lysine oxidase would successfully serve as a cross-linking agent in the invention of '957 because Stedronsky that lysine oxidase and transglutaminase are both suitable cross-linking enzymes.

Claims 1-10, 24, 36, 51 and 95-108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-52 of copending Application No. 11/144,372 in view of Stedronsky (US 6,258,872) and Webster's Dictionary.

The claims of '372 are drawn to a method for attaching a non-corneocyte protein, an agent, to a body comprising conjugating the agent to a carboxamide -containing linking molecule and then attaching he linked agent to the body tissue via transglutaminase. The claims meet the limitation in the instant application regarding the term "microparticle" because a microparticle is interpreted as a small part *supra* and non-corneocyte proteins are small parts of matter. '372 does not claim the employment of lysine oxidase to effect the crosslinking reactions. Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule, such as a protein, between said tissue and the adhesive/sealant. The agents can be cross-linked together by transglutaminase or lysine oxidase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute lysine oxidase for transglutaminase in the invention of '372. The ordinary artisan would have been motivated to do so because lysine oxidase and transglutaminase are equivalent alternatives for cross-linking of biological agents and proteins. The ordinary artisan would have had a reasonable expectation that lysine oxidase would successfully serve as a cross-linking agent in the invention of '957 because Stedronsky that lysine oxidase and transglutaminase are both suitable cross-linking enzymes.

This is a provisional obviousness-type double patenting rejection.

Claims 1-10, 24, 36, 51 and 95-111 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-50 of copending Application No. 11/125,830 in view of Stedronsky (US 6,258,872).

The claims of '830 are drawn to a method for attaching microparticles to the surface of the skin of a subject comprising conjugating microparticles to the skin via endogenous transglutaminase. '830 does not claim the employment of lysine oxidase, endogenously or exogenously, to effect the crosslinking reaction. Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule, such as a protein, between said tissue and the adhesive/sealant. The agents can be cross-linked together by transglutaminase or lysine oxidase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute lysine oxidase for the endogenous transglutaminase in the invention of '830. The ordinary artisan would have been motivated to do so because lysine oxidase and transglutaminase are equivalent alternatives for cross-linking of biological agents and proteins. The ordinary artisan would have had a reasonable expectation that lysine oxidase would successfully serve as a cross-linking agent in the invention of '830 because Stedronsky that lysine oxidase and transglutaminase are both suitable cross-linking enzymes.

This is a provisional obviousness-type double patenting rejection.

Claims 1-10, 24, 36, 51 and 95-108 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22, 25, 145-152, 155, 156, 158-165 and 167-173 of copending Application No. 09/620,783, now allowed, in view of Stedronsky (US 6,258,872).

The claims of '783 are drawn to a method for attaching microparticles to the body tissue of a subject comprising conjugating microparticles to the tissue via endogenous or exogenous

transglutaminase. The claims meet the limitation in the instant application regarding the term "agent" because a microparticle is an agent. '783 does not claim the employment of lysine oxidase, endogenously or exogenously, to effect the crosslinking reaction. Stedronsky discloses a method for enhancing the mechanical performance of tissue adhesives and sealants (referred to as adhesive/sealant) in damaged tissue by inserting a primer molecule, such as a protein, between said tissue and the adhesive/sealant. The agents can be cross-linked together by transglutaminase or lysine oxidase.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute lysine oxidase for the endogenous transglutaminase in the invention of '783. The ordinary artisan would have been motivated to do so because lysine oxidase and transglutaminase are equivalent alternatives for cross-linking of biological agents and proteins. The ordinary artisan would have had a reasonable expectation that lysine oxidase would successfully serve as a cross-linking agent in the invention of '783 because Stedronsky that lysine oxidase and transglutaminase are both suitable cross-linking enzymes.

This is a provisional obviousness-type double patenting rejection.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
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IRENE MARX
PRIMARY EXAMINER